Please add the following new claims:

--96. (New) The method of claim 85 wherein the tissue of interest is exposed to an amount greater than an effective amount of an agent.

97. (New) The method of claim 96 wherein the greater amount is a toxic amount of an agent.--

REMARKS

I. Summary of the Office Action

The Office Action acknowledged entry of the amendments to the title, specification and claims. Further, the Examiner acknowledged cancellation of claims 7-9.

In view of amendments/arguments, the objection to the title was withdrawn.

In view of amendments/arguments, the objection to the specification was withdrawn.

In view of amendments/arguments, the objection to claims 5, 10 and 12 was withdrawn.

Claims 1-6, 10-13 and 95 were rejected under 35 U.S.C. §112, second paragraph as allegedly being indefinite.

Claims 1-6, 10-13 and 85-95 were rejected under 35 U.S.C. §112, first paragraph as allegedly being not enabled.

Claims 1-13 and claim 95 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Anderson et al. (Electrophoresis (1991) 12:907-903) in view of Page et al. (DDT (1999) 4:55-62).

Claims 85-92 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Anderson et al. (1991).

II. Summary of the Response

Claims 1-6, 10-13 and 95 were cancelled. Claims 85, 86, 89, 91 and 93 were amended and claims 96-97 were added to describe more clearly the present invention.

Applicants traverse the outstanding rejections against claims 85-94 as amended-in-part and explain why the rejections do not apply to new claims 96-97.

III. Rejection Under 35 U.S.C. §112, Second Paragraph

Claims 1-6, 10-13 and 95 were rejected under 35 U.S.C. §112, second paragraph as allegedly being indefinite.

As claims 1-6, 10-13 and 95 were canceled, the rejection is moot. Regarding amended claims 85, 86, 89, 91 and 93 and new claims 96-97, the rejection is traversed and does not apply for the reasons below.

An issue was the term "efficacy." As stated in the previous Action, the term is well known and well recognized in the fields of pharmacology, toxicology and medicinal chemistry. The plain meaning of the term being, "the power to produce an effect" (see <www.m-w.com/cgi-bin/dictionary). Applicants apply no separate meaning, and look for effects over a range of concentrations, where for example, the concentration with the most potent effect would have the most efficacy. Thus, again, in response to the alleged

requirement to specifically define the term as intimated in the Action, respectfully no specific definition is needed as the term is applied with its usual meaning.

A requirement for defining said art recognized term, when such is used in its ordinary meaning, is not proper. Further, the Examiner would suggest that the "degree of efficacy is not defined." Applicants offer, for example, at page 23, lines 25-30:

> "The degree of its [cytosolic HMG-CoA synthase] induction thus may reflect the pharmacological potency of an HMG-CoA reductase inhibitor to inhibit HMG-CoA reductase and hence serves as a marker to compare efficacy among members of the statin family of compounds and between families of chemically unrelated agents with a similar mode of action." (Emphasis added).

Respectfully, such a disclosure meets the elements identified by the Examiner, i.e., 1) efficacy is related to induction of select proteins/peptides (in the example, HMG-CoA synthase), 2) a disorder, for example, may include cholesterol metabolism and 3) degree is related such that greater concentrations of drug result in finite quantitative changes in the amounts measured for various protein markers. (For example, within the statin family "greater concentrations of statins result in a greater alteration in the abundance of many of the protein markers," at page 23, line 31 to page 24, line 2). Therefore, Applicants submit that the term is not indefinite and neither does the phrase render the claim indefinite. An artisan would well recognize the meaning and scope of the term.

With respect to the phrase "not previously known to have toxicity or efficacy," while Applicants do not acquiesce to the reasoning offered in the Action, the recitation does not appear in any of the new or amended claims.

Regarding claim 94, the Examiner suggested that the claim is confusing, alleging "it is not clear whether the agent recited by the claim is 'a said known effective agent' recited in claim 93 or 'an agent candidate not previously known to have toxicity of [sic] efficacy' recited by claim 1, [sic] or both."

Applicants respectfully submit that, while not acquiescing to the reasoning offered by the Examiner, claims 94 (and claim 93) have been amended to more clearly define the invention. Further, Applicants submit that with respect to this aspect of the rejection, the metes and bound of the amended claims would be clear to the skilled artisan.

Applicants appreciate the suggestions offered by the Examiner.

Respectfully, in view of the arguments presented above, Applicants submit that the rejection does not apply to the pending claims.

IV. Rejections Under 35 U.S.C. §112, First Paragraph

Claims 1-6, 10-13 and 85-95 were rejected under 35 U.S.C. §112, first paragraph as allegedly being not enabled. As claims 1-6, 10-13 and 95 have been canceled, the rejection is moot. Regarding amended claims 85, 86, 89, 91 and 93 (including claims dependent therefrom) and new claims 96-97, the rejection does not apply for the reasons below.

The Examiner asserted that the disclosure is enabling "for determining changes in the presence of markers in a proteome, wherein changes are caused by exposure of a tissue to tested chemicals." Further, the Examiner alleged that the disclosure is not enabled for "quantifying a degree."

The rejection is traversed for the following reasons.

The plain meaning of degree is the extent, measure, or scope of an action, condition, or relation (see <www.m-w.com/cgi-bin/dictionary>, last visited on 27 January 2003).

The present application contains many recitations of the term "measure," including grammatical variations thereof. Further, the application specifically teaches means to measure or to quantify proteins (see for example, page 15, lines 18-26, which discloses how proteins of interest may be identified and quantified). Moreover, such measurements are tied to protein standards necessary to determine differences in concentration of other proteins and association of said differences with disease states and normal tissues. The results from such experiments are compared to generate differential results (e.g., presence or absence of drug treatment). Such measures are used in the proteomic techniques as disclosed to study proteome changes in biological samples (see, for example, for drug treated animals at page 21, line 15 to page 23, line 6).

While the Examiner recited one particular manner of measuring efficacy, it is not the only way. Nevertheless, the means envisaged for the instant application comprise quantitative measures of protein abundance to determine the power of a compound over a concentration range to produce an effect (i.e., efficacy).

With respect to toxicity, at minimum, the known compounds used in the instant invention have art recognized LD_{50}s (i.e., the measure of toxicity, for example Niacin is 5 g/kg in rats or Lovastatin is 15 g/m^2 in mice see, <www.advicor.com/p-prescription.html>, last visited 27 September 2003). Further, the specification clearly states ranges of use of different compounds, where the dose used exceeds the maximal dose recommended for

human use (see EXAMPLE 4, lines 8-16); in other words toxic dose equivalents. As the proteomic techniques would be utilized for toxic measurements as well as efficacy, so too would the identification and quantification of the protein standards and markers (*supra*).

Regarding the suggested lack of guidance, certainly the specification provides a process whereby using different concentrations of a drug in contact with a system, patterns of proteins emerge where the patterns associated with efficacy and toxicity of said drug are identified. Unknown compounds that produce similar patterns will likely have similar properties with respect to efficacy and toxicity on that system. The necessary information of how to obtain one or more markers to determine efficacy and toxicity in a system using the proteomic techniques and quantitative means clearly is recited in the specification. This is the process that is claimed.

Respectfully, the specification provides the guidance for one of skill to practice the invention as claimed and no more is required under the statute. Even though routine, mechanical, and/or tedious preparation may be involved, this is not undue.

In view of the arguments presented above, Applicants submit that the rejection does not apply to the pending or new claims and withdrawal thereof is in order.

V. Rejection Under 35 U.S.C. §103(a)

(A) Claims 1-13 and 95 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Anderson et al. (1991) in view of Page et al. (1999).

As claims 1-13 and 95 have been canceled, the rejection as it pertains to said claims is moot. Further, the rejection as recited does not apply to claims 85-94, 96 or 97, and is traversed for the following reasons.

The Examiner alleged that Anderson et al. teach a method of using specific agents that contact select animal tissues in conjunction with 2D electrophoresis for proteome analysis. Further, such analysis is suggested to result in the identification of markers which allegedly overlap with the markers as claimed. Moreover, the Examiner suggested that the reference is deficient in the failure to teach "as a control sample protein form [sic] the tissue exposed to compounds with known toxicity and efficacy, neither they [sic] use agents not tested previously."

The Action goes on to offer the teachings of Page et al. to cure such deficiency, suggesting Page et al. disclose that proteomics technology is being integrated into the drug discovery process, specifically that said technology is useful in formal drug toxicology studies.

But the claims are directed to a method of determining and no steps are disclosed in either cited reference that provide the recited step of using more than one concentration of compound. Data from single concentrations of drug exposure do not, a priori, demonstrate that a quantitative correlation exists between protein pattern changes and predictable drug effects.

Typical drug studies require measuring drug effects on protein activity (e.g., binding to the receptor and K_D), not measuring protein amount. No analysis of such data will lead

one of skill in the art to conclude that protein abundance is proportional to drug efficacy because only one concentration of the drug is being tested.

The instant invention uses multiple dosages to demonstrate drug induced proportional alterations of proteins concentration. This is unexpected because, in contrast to a chemical reaction, the results are predictive of system responses (i.e., an organism) to a drug.

The instant specification shows quantitative data as compared to qualitative data known in the art.

The basic argument is that a known pharmaceutical has an activity and one cannot determine whether a new compound is better, worse or the same than the known pharmaceutical unless you first establish that you have a quantitative measurement that corresponds to a pharmaceutical benefit.

The claims recite measuring the abundance of the protein marker, NOT the biological activity. There is no basis to conclude that one is proportional to the other.

Both cited references compare only untreated controls vs. drug treated, see Fig. 3 of Page et al. and the abstract of Anderson et al. The argument that it is obvious to observe changes in at least one protein concentration is not tenable because one cannot distinguish significance from noise. The 2-D electrophoresis process of the prior art and the present invention denatures the protein. Everyone is measuring protein amount not activity. No analysis of such data will lead one to conclude that protein abundance is proportional to drug efficacy because only one concentration is being tested.

The instant invention is the first to use multiple different dosages of a treatment (drug) and to show that the protein measurements are likewise altered in a somewhat

proportional manner. The instant invention does not relate to a chemical reaction but rather how a host responds to a drug. Biological response is frequently not proportional, especially once one reaches an effective dosage. For example, if one has a fever from the flu, the fever can be relieved with an aspirin or acetaminophen. Taking more aspirin will not lower the body temperature below 37° C. Also, the biological effect of the drug is saturated at some dose, usually the effective dosage. For aspirin and many other drugs, giving 10 times the effective dosage does not give a more effective response. The fever will still be reduced to 37° C. Therefore, one would not necessarily expect the protein abundance variation caused by the drug to be altered proportionally, especially when the drug is used in dosages above the effective dose.

Indeed, one might expect that some proteins would not be altered at all unless one used a toxic amount of drug. That is the theory proposed by Page et al, page 62, lines 7-13, but no experiments were ever done. It is not what was observed in the instant invention.

Given these competing theories of how the body would respond to a drug, and only one possible theory permits one to quantitatively compare a known effective drug and a candidate drug, there is no reasonable expectation of success by merely reading the cited references in view of the claimed invention.

Anderson et al. and Page et al. do not show any dose response effectiveness or toxicity at all. Indeed, each drug in each reference is used in only one concentration. By contrast, the current specification teaches that many proteins show a proportional or antiproportional response to using different concentrations of the same drug. Tables of some examples are below:

For example, in Table 2 of the specification, many examples are readily seen by simple scanning. Below are some examples from the first three proteins and the last three proteins in Table 2:

	Control	Low Dose	High Dose
MSN	AVOL	AVOL	AVOL
73	19379	18113	16433
101	13120	10860	9189
106	7287	6522	2822

The last three on table 2 are:

	Control	Low Dose	High Dose
MSN	AVOL	AVOL	AVOL
229	15082	13725	10693
413	4951	6944	14671
1250	547	672	2238

While the proportional change with changing pharmaceutical dosage does differ from protein to protein, the overall technique provides quantitative data.

As for actually comparing some of the data, the table below is a subset of the data in Table 2 of the specification. The data is to be interpreted for patentability purposes only. Applicants do not wish to make any comment good or bad about any of the three FDA approved drugs mentioned below.

	Mevacor			Zocor			Lescol		
MSN#	Con	Low	High	Con	Low	High	Con	Low	High
29	34250	32869	66259	36966	37735	87836	31559	36444	83438
113	17079	13248	11991	18595	19634	13417	17110	15940	11325
126	10311	11284	5748	11499	12740	7881	10805	9737	4289
142	18552	17006	10762	23893	20737	12642	20616	19066	9922

It can be seen that in response to differing concentrations of the drug, one can make these statements: Mevacor has a different pattern from the others for MSN 29. Zocor has a different pattern from the others for MSN 113. Lescol has a different pattern from the others for MSN 126. All have similar patterns for MSN 142.

Moreover, Page et al. have not shown any convincing evidence of quantitative proteomics. The differential analysis of MCI used in Page et al. is a statistical analysis to compensate for the relatively large CV resulting from the data. Because Page et al. used a relatively lower quantitative system with relatively lower reproducibility than in the present specification, standard statistical analysis does not work well for the Page et al. system unless one accepts a high P value. The differential analysis taught adds together the amounts of each protein for each sample within the group and compares it to the same from another group. One does not see the "Noisy" data with a very high coefficient of variability using the Page et al. analysis. For example, assume the data in the table below:

Amounts of protein X per sample

Sample #	control group	test group
1	1 mg	1 mg
2	1 mg	1 mg
3	1 mg	1 mg
4	1 mg	1 mg
5	1 mg	I mg
6	1 mg	I mg
7	1 mg	23 mg
8	1 mg	1 mg
9	1 mg	1 mg
10	1 mg	1 mg

Logically, one would suspect sample 7 of the test group as an experimental error. Even counting 7, by standard statistical analysis no significant difference would be found. However, by the data analysis of Page et al, that protein has over a 3-fold increase in the test group rather than the control group.

Likewise assume the data were:

Amounts of protein X per sample

Sample #	control group	test group
1	1 mg	0.1 mg
2	1 mg	10 mg
3	1 mg	0.1 mg
4	1 mg	10 mg
5	1 mg	0.1 mg
6	1 mg	10 mg
7	1 mg	0.1 mg
8	1 mg	10 mg
9	1 mg	0.1 mg
10	1 mg	10 mg

The analysis in Page et al. would show a 5-fold difference between test and control groups. However, the data actually shows no difference between the groups when considering

the variability. Note that the data were made with half of the values lowered by one order of magnitude and the other half increased by one magnitude.

In conclusion, Page et al. do not teach any quantitative proteometric measurements and therefore cannot reasonably teach making a quantitative comparison between the effects of one known drug and a compound having the same biological activity. By contrast, the instant specification is full of examples where the amounts of a protein are proportional or inversely proportional to the dosage of drug.

Applicants submit that Anderson et al., Page et al. or a combination of the two neither teaches nor suggests how to make quantitative comparisons between different compounds within the same class of biological activity.

Accordingly, withdrawal of the rejection is in order.

(B) Claims 85-92 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Anderson et al. (1991).

The rejection is traversed for the following reasons.

There is no specific suggestion for any of the specific claimed markers in Anderson et al. Moreover, Anderson et al. do not indicate the specific markers may be measured quantitatively in a manner that permits one to determine whether a candidate

compound is more or less effective and/or more or less toxic than a known pharmaceutical or toxic compound.

Anderson et al. showed that combining two different drugs, which act by unrelated mechanisms, can yield an unexpected variety of events. Synergistic results were observed for some proteins (Figures 10 and 11). The same drug combination gave no or modest results for other proteins (Figure 12). The same drug combination gave anti-synergistic (destructive) results for another protein (Figure 13). Thus you cannot conclude anything at all as to the relative effectiveness of a drug, the proteins affected and how the proteins are affected.

Thus, a prima facie case of obviousness as to the claimed invention has not been made. Accordingly, the rejection must be withdrawn.

CONCLUSION

The Examiner is thanked for the interview. The Summary provided by the Examiner is a thorough record of the substance of the interview.

Applicants have taken substantial steps to advance prosecution. Reexamination, reconsideration, withdrawal of the rejections and early indication of allowance are requested respectfully. If any questions remain, the Examiner is urged respectfully to contact the undersigned at the local exchange provided below.

The Commissioner hereby is authorized to charge payment of any fees under 37 C.F.R. §1.17 that may become due in connection with the instant application or credit any overpayment to Deposit Account No. 18-2220.

Respectfully submitted,

Dean H. Nakamura
Reg. No. 33,981

Roylance, Abrams, Berdo
& Goodman, L.L.P.
1300 19th Street, N.W., Suite 600
Washington, D.C. 20036-2680
(202) 659-9076

Dated: 12 February 2003

85. (Amended) A method for determining a degree of toxicity or efficacy of an agent comprising:

exposing a tissue of interest in a subject to the agent such that the agent contacts said tissue of interest,

obtaining a test biological sample containing protein from said tissue of interest,

measuring levels of at least one protein marker selected from the group consisting of Actin gamma, Adenosine kinase (EC 2.7.1.20), Adensylhomocysteinase, Alanine aminotransferase, Alpha 2μ-globulin, Annexin IV, Annexin VI, Antiquitin, Apolipoprotein A-I, Apolipoprotein E precursor, Catechol O-methyl transferase, Calreticulin, Catalase, Cytokeratin ends A, N-G, N-G-dimethylarginine dimethylaminohydrolase, D-dopachrome tautomerase, Epoxide hydrolase, soluble, ER60 protease; 58kD microsomal protein, Fatty acid binding protein, liver, Fructose-1,6-bisphosphatase (EC 3.1.3.11) (MSN 79), Fructose-1,6-bisphosphatase (EC 3.1.3.11) (MSN 182), Fructose-1,6-bisphosphatase (EC 3.1.3.11) (MSN 577), Fumarylacetoacetate hydrolase, 75kD glucose related protein, Glucose-6-phosphate 1-dehydrogenase (EC 1.1.1.49), Glutathione synthetase, 90kD heat shock protein, Heme oxygenase-1, Heterogeneous nuclear ribonucleoprotein K, HMG-CoA synthase, mitochondrial frag. (EC 4.1.3.5), HumorF06, N-hydroxyarylamine sulfotransferase (EC 2.8.2.-), 3-Hydroxyanthranilate 3,4-dioxygenase (EC 1.13.11.6), 4-Hydroxyphenylpyruvate dioxygenase, Induced in androgen-indep. prostate cells by eff. of apopt., Isopentenyl-diphosphate delta-isomerase (EC 5.3.3.2), Isovaleryl-CoA dehydrogenase, Keratin type II cytoskeletal 8 (MSN 97), Keratin type I cytoskeletal 18, Keratin type II cytoskeletal 8 (MSN 41), Ketohexokinase (EC 2.7.1.3), Lamin b, Major vault protein, Methionine adensyltransferase, 3-Mercaptopyruvate sulfotransferase (EC

2.8.1.2), 23kD Morphine-binding protein, Nucleolar phosphoprotein B23 (MSN 574), Nucleolar phosphoprotein B23 (MSN 671), 2-oxoisovalerate dehydrogenase alpha subunit, mitochrondrial, Peroxisomal enoyl hydratase-like protein, Phenylalanine hydroxylase (EC 1.14.16.1), Protein kinase C inhibitor, Pyruvate kinase, isoenzymes (MSN 282), pyruvate kinase L, Ras-GTPase-activating protein SH3-domain binding protein, Senescence marker protein-30 (MSN 55), Senescence marker protein-30 (MSN 103), Serine protease inhibitor 2, Tropomysin, MSN 42, MSN 59, MSN 66, MSN 69, MSN 73, MSN 76, MSN 83, MSN 117, MSN 122, MSN 127, MSN 128, MSN 139, MSN 143, MSN 148, MSN 154, MSN 155, MSN 197, MSN 203, MSN 218, MSN 229, MSN 232, MSN 237, MSN 238, MSN 261, MSN 267, MSN 268, MSN 275, MSN 279, MSN 286, MSN 270, MSN 289, MSN 292, MSN 297, MSN 310, MSN 311, MSN 318, MSN 322, MSN 339, MSN 350, MSN 358, MSN 362, MSN 365, MSN 371, MSN 372, MSN 379, MSN 384, MSN 395, MSN 399, MSN 416, MSN 420, MSN 423, MSN 427, MSN 434, MSN 435, MSN 438, MSN 461, MSN 469, MSN 479, MSN 492, MSN 497, MSN 502, MSN 506, MSN 510, MSN 522, MSN 546, MSN 556, MSN 557, MSN 565, MSN 569, MSN 571, MSN 578, MSN 602, MSN 605, MSN 613, MSN 618, MSN 625, MSN 637, MSN 644, MSN 646, MSN 653, MSN 665, MSN 666, MSN 669, MSN 681, MSN 689, MSN 718, MSN 719, MSN 721, MSN 777, MSN 779, MSN 787, MSN 802, MSN 806, MSN 810, MSN 839, MSN 876, MSN 879, MSN 887, MSN 888, MSN 900, MSN 905, MSN 966, MSN 984, MSN 1065, MSN 1081, MSN 1053, MSN 1172, MSN 1195, MSN 1215, and MSN 1255,

[the markers of Table 8 except for MSN 34, MSN 79, MSN 182, MSN 204, MSN 347, MSN 413, MSN 633, MSN 933, MSN 1001 and MSN 1250.]

and

comparing the levels of said markers to the levels of the same markers in a control sample or other sample exposed to a known toxic or a known effective [agents] agent to determine whether the tissue of interest in a subject is experiencing toxicity or an effective response or the degree of such responses.

86. (Amended) The method of claim 85 wherein said protein marker is selected from the group consisting of MSN 34, MSN 42, MSN 59, MSN 66, MSN 69, MSN 73, MSN 76, MSN 83, MSN 117, MSN 122, MSN 127, MSN 128, MSN 139, MSN 143, MSN 148, MSN 154, MSN 155, MSN 197, MSN 203, MSN 218, MSN 229, MSN 232, MSN 237, MSN 238, MSN 261, MSN 267, MSN 268, MSN 275, MSN 279, MSN 286, MSN 270, MSN 289, MSN 292, MSN 297, MSN 310, MSN 311, MSN 318, MSN 322, MSN 339, MSN 350, MSN 358, MSN 362, MSN 365, MSN 371, MSN 372, MSN 379, MSN 384, MSN 395, MSN 399, MSN 416, MSN 420, MSN 423, MSN 427, MSN 434, MSN 435, MSN 438, MSN 461, MSN 469, MSN 479, MSN 492, MSN 497, MSN 502, MSN 506, MSN 510, MSN 522, MSN 546, MSN 556, MSN 557, MSN 565, MSN 569, MSN 571, MSN 578, MSN 602, MSN 605, MSN 613, MSN 618, MSN 625, MSN 637, MSN 644, MSN 646, MSN 653, MSN 665, MSN 666, MSN 669, MSN 681, MSN 689, MSN 718, MSN 719, MSN 721, MSN 777, MSN 779, MSN 787, MSN 802, MSN 806, MSN 810, MSN 839, MSN 876, MSN 879, MSN 887, MSN 888, MSN 900, MSN 905, MSN 966, MSN 984, MSN 1065, MSN 1081, MSN 1053, MSN 1172, MSN 1195, MSN 1215, and MSN 1255 [of markers of Table 9 except for MSN 204, MSN 347, MSN 633 and MSN 1001].

89. (Amended) The method of claim 87 wherein the levels of protein markers in the test biological sample are compared to the levels of the same protein markers in biological samples exposed to a known effective agent or a known toxic agent.

91. (Amended) The method of claim 90 wherein the [agent] pharmaceutical is an antilipemic agent.

93. (Amended) The method of claim 85 [10] wherein the agent is a pharmaceutical suspected of having the same mechanism of action as said known effective agent and is given in a pharmaceutically appropriate amount.

94. (Amended) The method of claim 93 wherein the [agent] pharmaceutical is an antipipemic agent.